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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KATTEN MUCHIN ROSENMAN LLP
525 WEST MONROE STREET
CHICAGO, IL 60661-3693

EXAMINER	
CHONG, YONG SOO	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 02/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/092,083	MCCALLISTER ET AL.	
	Examiner	Art Unit	
	Yong S. Chong	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *44-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

This Office Action is in response to applicant's arguments filed on 12/29/2005. Claims 44-52 are pending and examined herein. Applicant's arguments have been fully considered but found persuasive to withdraw the 112-1st rejection and the claim objection only, however the 103(a) rejections are maintained for reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in Graham vs John Deere Co., 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 44-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Katdare et al. (5,853,759, of record).

Katdare et al. discloses that bisphosphonates including instant preferred bisphosphonates such as alendronate are known to have utility as pharmaceutical

agents for inhibiting bone resorption (see col. 1, lines 14-42). Katdare et al. particularly discloses that a composition be administered orally comprising the instant preferred bisphosphonate, alendronate, is known to be useful in a method of treating osteoporosis in postmenopausal women (human mammals) (see col.1, lines 43-49). The disclosed pharmaceutical effervescent formulations of alendronate therein in tablet and powders which are placed in an convenient amount of water to produce effervescent liquid (solution), and that the patient drinks the effervescent solution, are for eliminating or minimizing side effects during the medication (i.e., for treating osteoporosis and/or inhibiting bone resorption in a mammal) (see col.1, lines 8-1 1 and 48-57, col.2 lines 63-67). The particular disclosed alendronate effervescent compositions of Katdare et al. in Example 1-4 comprises alendronate in an effective amount (known for treating osteoporosis and/or inhibiting bone resorption), the instant preferred acid component, citric acid, and the instant preferred alkaline effervescing component, sodium bicarbonate and sodium carbonate, flavoring agent or sweetener and color agent, and then an convenient amount of water added to produce effervescent solution to be administered orally (see Example 1 at col.4 line 34-35 and 46-56 in particular), and the composition also comprises a lubricant such as sodium benzonate and polyethylene glycol (PEQ) (also known as a solubilizing agent (see col.2 lines 24-26 and col.4 lines 21-33).

Note that the total weight of the solid composition of Katdare et al. in claims 4-5 therein is 3.365 g, very close to 3.5 g as instantly claimed (see claims 4-5, adding up the weight of all solid ingredients. Moreover, the total weight of the table is known to

range from about 100 to about 50,000 mg, about 1500-32500 mg, or about 20,800-30,150 mg (see col.3, lines 1-5).

The weight percentage of the acid component in Example 1 is 58.7 wt % (which is calculated by 650 mg of citric acid per 1106.5 mg of total weight, see Example 1 at col.4), which is substantially close to about 51-52 wt %, the instant claimed range; the weight percentage of the alkaline component in Example 1 is 36.8 wt % (which is calculated by 367+40 mg of sodium bicarbonate and sodium carbonate, per 1106.5 mg of total weight, see Example 1 at col.4), within the instant claimed range. 34-38 wt %. The amount of bisphosphonate such as alendronate in the prior art composition ranges from 1 to 80 mg, overlapping with the instant claim.

Regarding the inherent property, the pH of the solution, it is noted that citric acid is employed in an excess in the composition therein to efficiently generate the effervescence and to sequester any ions to complex with alendronate, and to enhance favor as well, disclosed by Katdare et al. (see col.3 lines 60-65). Thus, the solution therein is acidic. The pKa of citric acid (known to used as a buffer), pK1, K2, K3 are 3.128, 4.761, and 6.396, respectively (provided by Bull "An Introduction to Physical Biochemistry" page 103, PTO-892). Thus, one of ordinary skill in the art would clearly recognize that the pH values in citric acid buffered solutions would be within the instantly claimed range about 4.5 to about 5.5, as shown in the calculation below: Example I discloses that citric acid is 650 mg and the molecular weight (or formula weight, FW) of citric acid is 192.12 (provided by Aldrich Handbook page 436, PTO-892). Thus, the moles of citric acid is 650 + 192.12 = 3.38 mmol.

Example I discloses that sodium bicarbonate is 367 mg and the molecular weight of sodium bicarbonate is 84.01 (provided by Aldrich Handbook page 1505, PTO-892). Thus, the moles of sodium bicarbonate is 367 + 84.01= 4.37 mmol.

Example I discloses that sodium carbonate is 40 mg and the molecular Weight of sodium carbonate is 105.99 (provided Aldrich Handbook page 1498, PTO-892). Thus, the moles of sodium carbonate is 40 + 105.99 =0.38 mmol.

It is known in the basic chemistry that the mole ratio of citric ac carbonate for neutralizing citric acid by sodium carbonate (or known as equal equivalent) is 2:3 (see col.3 line 67 to col.4 line 1) and the mole ratio of citric acid to sodium bicarbonate for neutralizing citric acid by sodium bicarbonate is 1:3.

Thus, 4.37 mmol of sodium bicarbonate neutralizes 4.87 X 1/3 = 1 .46 mmol of citric acid;

2.65 mmol of sodium carbonate neutralizes 0.38 X 2/3 = 0.25 mmol of citric acid;

Therefore, the left or excess of citric acid in the solution

= 3.38 - (1 .46 + 0.25) =1.67 mmol.

Therefore, 1.67 mmol, about a half amount of citric acid is free and left in the solution. Thus, the solution is acidic. As discussed above, according the known pKa values of citric acid, the pH value of the effervescent composition of Example 1 could be within the instant claim.

Moreover, after administering of the effervescent sotution of Katdare et al., the pH of the mammal's stormach would be inherently raised to the range here since the citric acid solution is a known buffered soiution which would mediate the pH in the

mammal's stomach for a period of time.

Thus, oral administration of Kuznicki's effervescent composition to a mammal is useful in methods of treating osteoporosis and inhibiting bone resorption.

Katdare et al. does not expressly disclose that the total weigh of the solid compositions of the prior art is about 4.3 to about 6 grams such as 5000 mg (4.350 or 5 grams). Katdare et al. does not expressly disclose that the acid component is about 51-52 wt % by weight of solid compositions of the prior art.

It would have been obvious to a person of ordinary skill in the ad at the time the invention was made to determine or optimize the total weigh of the solid compositions of the prior art to about 4.3 to about 6 grams such as 4.350 or 5 g, and the acid component to about 51-52% by weight of solid compositions.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine or optimize the total weigh of the solid compositions of the prior art to about 4.3 to about 6 grams, since the claimed range 4.3 to about 6 grams lies inside ranges disclosed by the prior art, about 100 to about 50,000 mg, about 1500 - 32500 mg, or about 20,800 - 30,150 mg. Thus, a prima facie case of obviousness exists. See In re Wertheim, 541 F.2d 257, 191 USPQ 90 (CCPA 1976)., In re Woodruff, 919 F.2d 1575, 16 USPQZd 1934 (Fed. Cir. 1990). See also MPEP 2144.05.

Additionally, one having ordinary skill in the art at the time the invention was made would have been motivated to adjust the acid component to about 51-52% by weight of solid compositions since the weight percentage of the acid component

disclosed by Katdare et al. in Example 1 is 58.7 wt % is substantiallv close to about 51-52 wt %, the instant claimed range. Moreover, the determination or optimization of amounts of a known acid compound to be used to adiust the known pH of the buffering composition based on the prior art teachings, is considered well within conventional skills in pharmaceutical science, involving merely routine skill in the art.

It has been held that it is within the skills in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See In re Boesch, 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the teachings of the prior art.

Claims 44-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daifotis et al. (5,994,329, of record).

Daifotis et al. discloses the compositions of a bisphosphonate comprising a bisphosphonate including instant preferred bisphosphonates such as alendronate, in oral forms therein such as in effervescent compositions, and also comprising solubilizing-agents-such as polyvinylpyrrolidone, coloring agents, and sweeteners (see. col.I lines 15-58, col. 11 line 55 to col.12 lines 3, c61.12 lines 3-34), especially the liquid formulation or composition of Example 8 employed in the methods of treatments herein in Examples 2-6 comprising alendronate salt in the amounts within the instant claim (see col.5 lines 44-45, Example 8 at col.19), the instant preferred acid component, citric acidand sodium citrate, and an alkaline component is used to adjust the pH of the solution formulation to 6.75 (reads on the instant claim, about 6.5)(see particular

Example 8 at col. 19 lines 40-62,). These compositions of a bisphosphonate be administered orally are useful for methods of treating osteoporosis and bone resorption in human mammals such as postmenopausal women (see also abstract, col.5 lines 21-23 and 29-35, col.7 lines 31-37, and examples 2-6 at col.17-18).

Daifotis et al. further discloses that the methods and bisphosphonate compositions therein also comprise a histamine H2 receptor blocker (Hz-antagoinsts), e.g., cimetidine, famotidin, and nizatidine, which are the instant preferred anti-ulcer agents, in order to minimize adverse gastrointestinal effects produced by a bisphosphonate (see col.13 lines 21-46).

Daifotis et al. does not expressly disclose that the total weight of the solid compositions of the prior art is about 4.3 to about 6 grams such as 4.3 or 5 grams. Daifotis et al. does not expressly disclose that the acid component is about 51-52 % by weight of solid compositions of the prior art. Daifotis et al. does not expressly disclose the pH range claimed herein.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to determine or optimize the total weigh of the solid compositions of the prior art to 4.3 to about 6 grams, and the acid component to about 51-52 % by weight of solid compositions.

One having ordinary skill in the art at the time the invention was made would have been motivated to determine or optimize the total weight of the solid compositions of the prior art to 4.3 to about 6 grams, since determining or optimizing the known amounts of bisphosphonate, solubilizing agents such as polyvinylpyrrolidone, coloring

agents, and sweeteners in a pharmaceutical composition, and the determination or optimizatiop of amounts of a known acid compound to be used to adiust the known pH of the buffering composition based on the prior art teachings, are considered well within conventional skills in pharmaceutical science, involving merely routine skill in the ad. Moreover, after administering of the liquid composition of Example 8 in Daifotis et al., the pH of the mammal's stomach would be inherently raised to about the claimed range since the citric acid solution is a known buffered solution which would mediate the pH in the mammal's stomach for a period of time.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See In re Boesch. 205 USPQ 215 (CCPA 1980).

Thus the claimed invention as a whole is clearly prima facie obvious over the teachings of the prior art.

Response to Arguments

Applicants argue that the combination of pH and buffering capacity is not disclosed by Katdare et al. Applicant also argues that Katdare et al. formulas all have total weights that lie just below the claimed weight ranges of 4.35 to 6 grams.

Examiner respectfully notes that the pH and buffering capacity are properties of a composition that is given little patentable weight if the general components of the same composition are met. Moreover, Katdare et al. disclose 3.365 g in claims 4-5 and in general about 100 to about 50,000 mg as the total weight range for the composition,

which substantially encompasses the claimed weight range in order to optimize the composition.

Furthermore, the optimization of amounts of a known acid compound to be used to adjust the known pH of the buffering composition based on prior art teachings, is considered well within the conventional skills in pharmaceutical science, involving mere routine skill in the art.

It has been held that it is within the skill in the art to select optimal parameters, such as amounts of ingredients, in a composition in order to achieve a beneficial effect. See *In re Boesch*, 205 USPQ 215 (CCPA 1980).

Applicant argues that Daifotis et al. contains no effervescing alkaline component. Examiner respectfully disagrees since Daifotis et al. discloses that the compositions are effervescent (col. 12, line 3) and can contain alkaline metals (col. 10, line 45).

In response to the Rohrich declaration stating that example 8 disclosed by Katdare et al. is not effervescent, Examiner responds by stating that it would have been obvious to use an alkaline metal such as sodium carbonate or sodium bicarbonate in both the compositions of Katdare and Daifotis et al. since both disclose effervescent compositions.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong S. Chong whose telephone number is (571)-272-8513. The examiner can normally be reached on M-F, 9-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SREENI PADMANABHAN can be reached on (571)-272-0629. The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SHENGJUN WANG
PRIMARY EXAMINER

YSC